



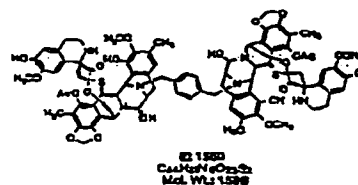
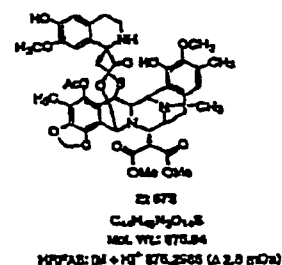
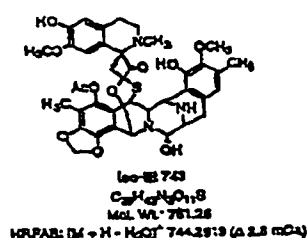
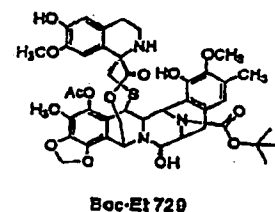
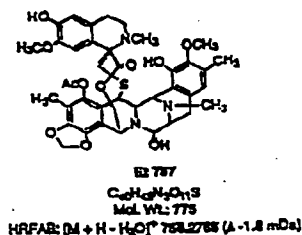
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(54) Title: SEMI-SYNTHETIC ECTEINASCIDINS

(57) Abstract

The present invention is directed to several newly prepared semi-synthetic ecteinascidin (Et) species, designated herein as Et 757, Boc-Et 729, Iso-Et 743, Et 875, and Et 1560. The physical properties of these compounds, their preparation and bioactivities are also reported.



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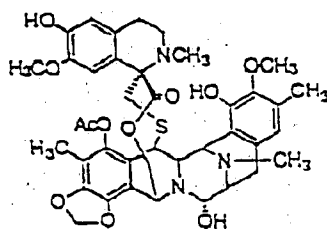
SEMI-SYNTHETIC ECTEINASCIDINS

BACKGROUND OF THE INVENTION

The ecteinascidins (herein abbreviated Et or Et's) are exceedingly potent antitumor agents isolated from the marine tunicate *Ecteinascidia turbinata*. In particular, Et's 729, 743 and 722 have demonstrated promising efficacy *in vivo*, including activity against P388 murine leukemia, B16 melanoma, Lewis lung carcinoma, and several human tumor xenograft models in mice. The antitumor activities of Et 729 and Et 743 have been evaluated by the NCI and recent experiments have shown that Et 729 gave 8 of 10 survivors 60 days following infection with B16 melanoma. In view of these impressive results, the search for additional ecteinascidin compounds continues.

SUMMARY OF THE INVENTION

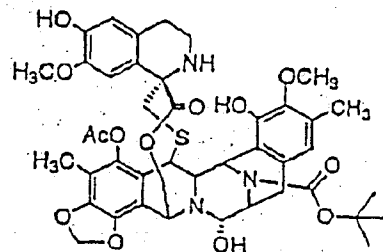
The present invention is directed to several new ecteinascidin compounds, prepared semi-synthetically, i.e., using previously discovered ecteinascidin compounds as the starting materials therefor. The structures of the new Et's of the present invention are as shown below:



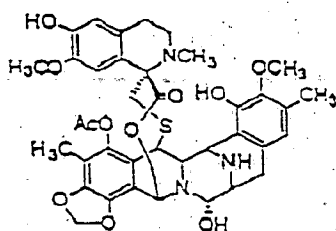
Et 757

 $C_{40}H_{43}N_3O_{11}S$

Mol. Wt.: 775

HRFAB: $[M + H - H_2O]^+$ 753.2765 (Δ -1.8 mDa)

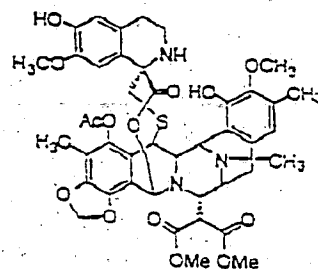
Boc-Et 729



Iso-Et 743

 $C_{39}H_{43}N_3O_{11}S$

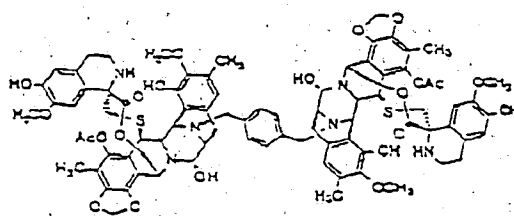
Mol. Wt.: 761.25

HRFAB: $[M + H - H_2O]^+$ 744.2619 (Δ 2.8 mDa)

Et 873

 $C_{40}H_{43}N_3O_{14}S$

Mol. Wt.: 875.94

HRFAB: $[M + H]^+$ 875.2986 (Δ 2.8 mDa)

Et 1560

 $C_{62}H_{69}N_6O_{22}S_2$

Mol. Wt.: 1535

The new ecteinascidin compounds shown above have been found to possess similar antitumor activity profiles as the known ecteinascidin compounds, and as such they will be useful as therapeutic compounds, e.g., for the treatment of mammalian tumors including

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melanoma, lung carcinoma, and the like. The dosages and routes of administration will vary according to the needs of the patient and the specific activity of the active ingredient. The determination of these parameters is within the ordinary skill of the practicing physician.

BRIEF DESCRIPTION OF THE DRAWINGS

Figures 1A and 1B show the LRFAB Mass Spectrum of Et 757 in Magic Bullet (MB). See, Rinehart et al., *Biochem. Biophys. Res. Commun.*, 1984, 124, 350.

Figures 2A and 2B show the tandem FABMS/MS spectrum of Et 757 in MB.

Figure 3 shows the ^1H NMR (500 MHz) spectrum of Et 757 in CD_3OD .

Figures 4A and 4B show the LRFAB Mass Spectrum of Et 729 in MB.

Figures 5A and 5B show the tandem FABMS/MS spectrum of Boc-Et 729 in MB.

Figure 6 shows the LRFAB Mass Spectrum of Iso-Et 743 in MB.

Figures 7A and 7B show the tandem FABMS/MS spectrum of Iso-Et 743 in MB.

Figure 8 shows the ^1H NMR (500 MHz) spectrum of Iso-Et 743 in CD_3OD .

Figure 9 shows expansion of the HMBC (750 MHz) spectrum of Iso-Et 743 in CD_3OD .

Figures 10A and 10B show the LRFAB Mass Spectrum of Et 875 in MB.

Figures 11A and 11B show the tandem FABMS/MS spectrum of Et 875 in MB.

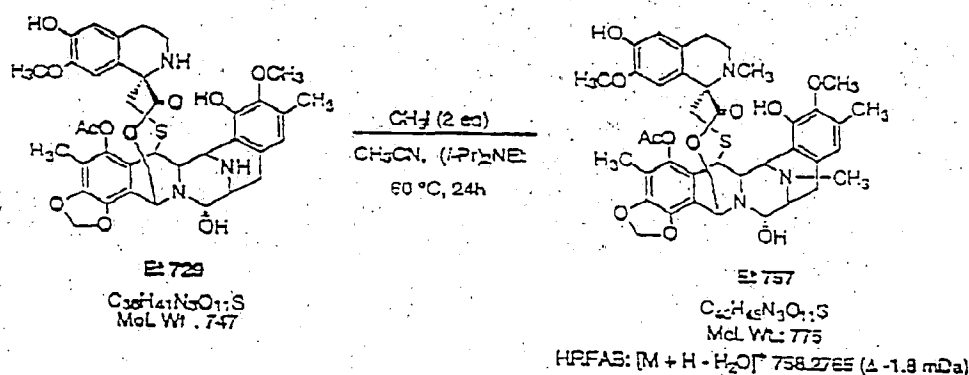
Figure 12 shows the LRFAB Mass Spectrum of Et 1560 in MB.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

As described above, a number of bioactive ecteinascidin compounds have been isolated from specimens of *Ecteinascidia turbinata*. See for example Ecteinascidins 729, 743, 745, 759A, 759B and 770, disclosed in U.S. Patent Nos. 5,089,273 and 5,256,663, the disclosures of which are hereby incorporated herein by reference. See also, Ecteinascidins 736 and 722, disclosed in U.S. Patent No. 5,149,804, which is hereby incorporated herein by reference. See also, U.S. Patent Nos. 5,478,932 and 5,654,426, which are hereby incorporated herein by reference.

The present invention will be further illustrated with reference to the following examples which aid in the understanding of the present invention, but which are not to be construed as limitations thereof. All percentages reported herein, unless otherwise specified, are percent by weight. All temperatures are expressed in degrees Celsius.

Example 1 - Semi-synthesis of Et 757

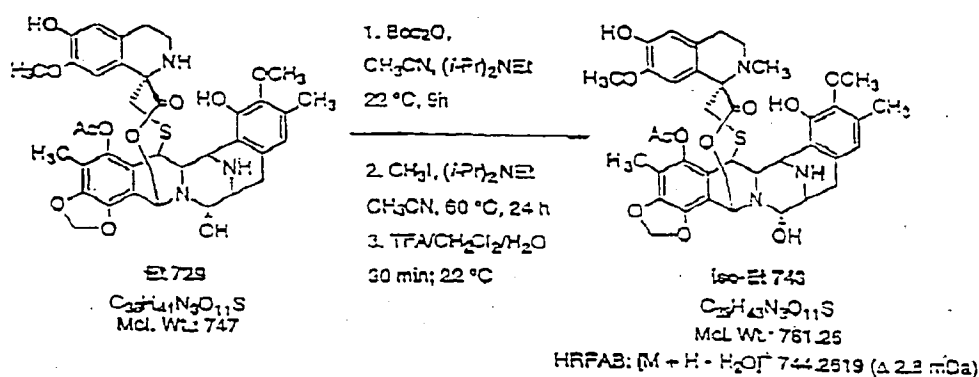


To a solution of Et 729 (9.2 mg, 0.012 mmol, 1 eq), diisopropylamine (12.9 μL , 0.074 mmol, 6 eq) and CH_3CN (300 μL) was added CH_3I (1.5 μL , 0.024 mmol, 2 eq) and the resulting solution was stirred at $60^\circ C$ for 24 hours. The reaction mixture was concentrated to dryness under a nitrogen stream. The residue was purified by reversed phase HPLC (Phenomenex/Ultracarb-ODS, 2 mL/min) using 75% MeOH/ H_2O containing 0.02 M NaCl as mobile phase to yield Et 757 (2.2 mg, 24%) and Et 743 (2.3 mg, 25%) and a complex mixture

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of permethylated products. Et 757 was further purified by HPLC (Ultracarb-ODS) using 60% MeOH/H₂O with 0.02 M NaCl as mobile phase to afford pure Et 757 (1.4 mg, 15%). HRFABMS, Calcd for C₄₀H₄₄N₃O₁₀S [M + H - H₂O]⁺ *m/z* 758.2747, Found 758.2765, see Figs. 1 and 2; ¹H NMR, see Fig. 3.

Example 2 - Semi-synthesis of Iso-Et 743



Step A - Boc-Et 729

To a solution of Et 729 (12.5 mg, 0.017 mmol, 1 eq), diisopropylethylamine (1.5 μL, 0.07 mmol, 4 eq) and CH₃CN (300 μL) was added di-*tert*-butyl dicarbonate (3.6 mg, 0.017 mmol, 1.0 eq) and the resulting solution was stirred at room temperature for 9 hours. The reaction mixture was concentrated to dryness under a nitrogen stream. The residue was purified by flash chromatography (gradient elution: 100% CHCl₃ ----> 90% CHCl₃/MeOH) to afford Boc-Et 729 (11.6 mg, 91%, *R_f* 0.53 in 90% CHCl₃/MeOH); HRFABMS, Calcd for C₄₃H₄₃N₃O₁₂S [M + H]⁺ *m/z* 850.2958, Found 850.2942, see Figs. 4 and 5.

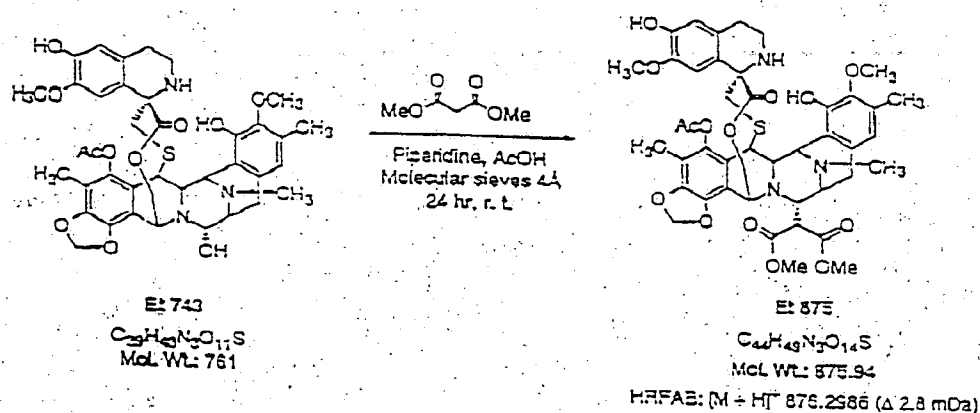
Step B - Iso-Et 743

To a reaction flask containing Boc-Et 729 (11.6 mg, 0.014 mmol, 1 eq), diisopropylethylamine (7.1 μL, 0.041 mmol, 3 eq), 500 μL of CH₃CN and a magnetic stirrer was added CH₃I (2.1 mg, 0.015 mmol, 1.1 eq), and the resulting solution was stirred at 60°C for 24 hours. The reaction mixture was concentrated to dryness under a nitrogen stream, then

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700 μ L of TFA/ CH_2Cl_2 / H_2O (4:1:1) was added. After the mixture was stirred at room temperature for 30 minutes, it was concentrated to dryness under a nitrogen stream. The residue was purified by reversed phase HPLC (Alltech-C18, 2 mL/min) using 60% MeOH/ H_2O containing 0.02 M NaCl as mobile phase to yield Iso-Et 743 (1.9 mg, 28%, based upon recovered Et 729) and unreacted Et 729 (3.6 mg). HRFABMS, Calcd for $\text{C}_{39}\text{H}_{42}\text{N}_3\text{O}_{10}\text{S}$ $[\text{M}+\text{H}-\text{H}_2\text{O}]^+ m/z$ 744.2591, Found 744.2619, see Figs. 6 and 7; ^1H NMR and HMBC, see Figs. 8 and 9 respectively.

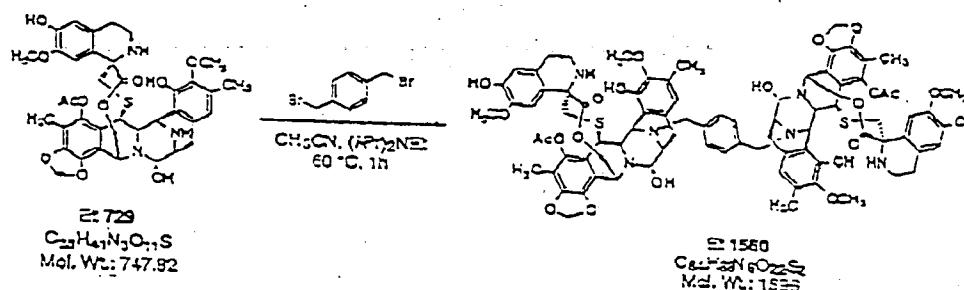
Example 3 - Semi-synthesis of Et 875



Glacial acetic acid (5 μ L of a 28% AcOH/ CH_3CN solution, 4 eq) was added to a mixture of Et 743 (0.9 mg, 0.001 mmol, 1 eq), piperidine (5 μ L of a 2% piperidine/ CH_3CN solution, 0.001 mmol, 1 eq), dimethyl malonate (5 μ L of a 3% dimethyl malonate/ CH_3CN solution, 0.001 mmol, 1 eq) and crushed activated 4 Å molecular sieves (~0.5 mg) in CH_3CN and the resulting suspension was stirred at room temperature for 24 hours. The reaction was filtered and the filtrate was concentrated to dryness. The residue was purified by flash chromatography (gradient elution: 100% CHCl_3 ----> 90% CHCl_3 /MeOH) to yield Et 875 (180 μ g, 20%, R_f 0.53 in 90% CHCl_3 /MeOH); HRFABMS, Calcd for $\text{C}_{44}\text{H}_{50}\text{N}_3\text{O}_{14}\text{S}$ $[\text{M}+\text{H}]^+ m/z$ 876.3013, Found 876.2986, see Figs. 10 and 11.

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Example 4 - Semi-synthesis of Et 1560 (Et 729 dimer)



To a reaction flask containing Et 729 (2.4 mg, 0.0032 mmol, 2 eq), diisopropylamine (2 μ L) and CH_3CN (75 μ L) and a magnetic stirrer was added α,α' -dibromo-*p*-xylene (34 μ L) of a 12.5 μ g/ μ L α,α' -dibromo-*p*-xylene/ CH_3CN solution, 0.0016 mmol, 1 eq) and the resulting solution was stirred at $60^\circ C$ for 1 hour. The reaction mixture was concentrated to dryness under a nitrogen stream. The residue purified by flash chromatography (gradient elution: 100% $CHCl_3$ ----> 90% $CHCl_3/MeOH$) to yield Et 1560 (300 μ g, 12%, R_f 0.53 in 90% $CHCl_3/MeOH$); HRFABMS, Calcd for $C_{58}H_{82}N_4O_{22}S_2$ $[M + H - 2H_2O]^+$ m/z 1561.5260. Found 1561.5221, see Fig. 12.

BIOLOGICAL ACTIVITIES

As described above, the ecteinascidins are highly functionalized bis- or tris-(tetrahydroisoquinoline) alkaloids that exhibit potent *in vivo* antitumor activity. These compounds have chiefly been isolated as natural products from the mangrove tunicate *Ecteinascidia turbinata*, which grows throughout the Caribbean and the Gulf of Mexico. The major product of most extractions, Et 743, is currently undergoing Phase I clinical trials for treatment of human solid tumors. See for example, Kuffel et al., *Proceedings of the American Association for Cancer Research*, 38: 596 (1997); Moore et al., *Proceedings of the American Association for Cancer Research*, 38: 314 (1997); Mirsalis et al., *Proceedings of the American Association for Cancer Research*, 38: 309 (1997); Reid et al., *Cancer*

Chemotherapy and Pharmacology, 38: 329-334 (1996); Faircloth et al., *European Journal of Cancer*, 32A, Supp. 1, pp. S5 (1996); Garcia-Rocha et al., *British Journal of Cancer*, 73: 875-883 (1996); Eckhardt et al., *Proceedings of the American Association for Cancer Research*, 37: 409 (1996); and Hendriks et al., *Proceedings of the American Association for Cancer Research*, 37: 389 (1996).

In view of the exceptional antitumor properties of the natural ecteinascidins, the present invention has studied the antitumor activities of the semi-synthetic analogs prepared herein. Table I shows the *in vitro* cytotoxic activities of the new Et compounds compared to the activity of two natural products, Et 743 and Et 729:

TABLE I

| Compound Name | Cytotoxicity to L1210 murine leukemia | |
|---------------|---------------------------------------|--|
| | IC ₅₀ | IC ₅₀ (Et 743)/IC ₅₀ |
| Et 729 | 0.05 | 10 |
| Et 743 | 0.5 | 1 |
| Et 757 | 0.01 | 50 |
| Iso-Et 743 | 0.03 | 17 |
| Boc-Et 729 | 5.0 | 0.1 |
| Et 1560 | 2.0 | 0.25 |
| Et 875 | 0.5 | 1 |

As shown by the *in vitro* data presented in Table I, the new compounds of the present invention possess cytotoxic activities levels up to 10 times better than those of two natural ecteinascidin compounds. Accordingly, it is expected that these compounds will also prove useful as pharmaceutical compositions for the treatment of mammalian, and particularly, human tumors *in vivo*.

REFERENCES

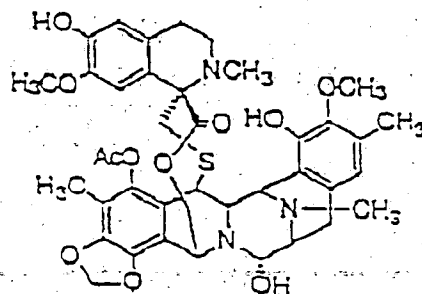
The following publications are cited as additional background information. To the extent necessary to allow a complete understanding of this invention, each is hereby incorporated herein by reference:

1. Rinehart, K.L. et al., *J. Nat. Prod.*, **53**: 771-791 (1990).
2. Wright, A.E. et al., *J. Org. Chem.*, **55**: 4508-4512 (1990).
3. Sakai et al., *Proc. Nat. Acad. Sci. U.S.A.*, **89**: 11456-11460 (1992).
4. Rinehart et al., *J. Org. Chem.*, **55**: 4512-4515 (1990).

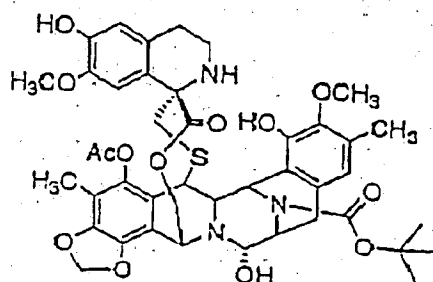
The present invention has been described in detail, including the preferred embodiments thereof. However, it will be appreciated that those skilled in the art, upon consideration of the present disclosure, may make modifications and/or improvements on this invention and still be within the scope and spirit of this invention.

WHAT IS CLAIMED IS:

1. The compound Et 757, which has the following structure:

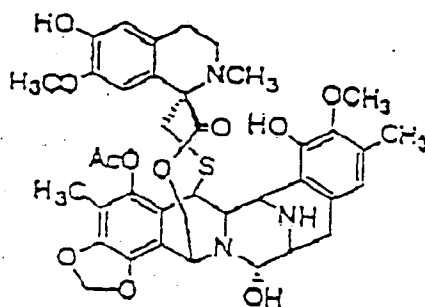


2. The compound Boc-Et 729, which has the following structure:

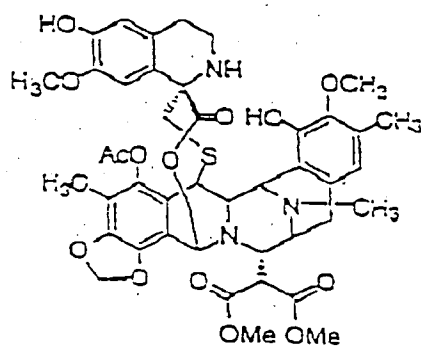


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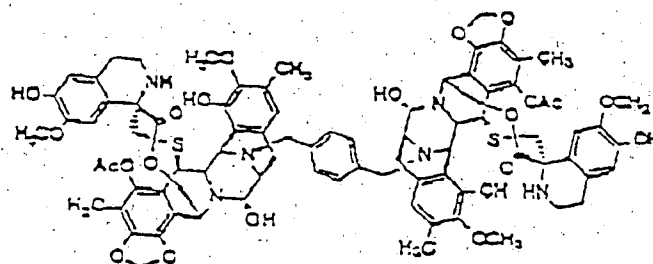
3. The compound Iso-Et 743, which has the following structure:



4. The compound Et 875, which has the following structure:



5. The compound Et 1560, which has the following structure:



6. A pharmaceutical composition comprising the compound Et 757 and a pharmaceutically acceptable diluent, carrier, or excipient.
7. A pharmaceutical composition comprising the compound Boc-Et 729 and a pharmaceutically acceptable diluent, carrier, or excipient.
8. A pharmaceutical composition comprising the compound Iso-Et 743 and a pharmaceutically acceptable diluent, carrier, or excipient.
9. A pharmaceutical composition comprising the compound Et 875 and a pharmaceutically acceptable diluent, carrier, or excipient.
10. A pharmaceutical composition comprising the compound Et 1560 and a pharmaceutically acceptable diluent, carrier, or excipient.
11. A method of treating a patient suffering from a mammalian tumor selected from the group consisting of mammalian leukemia, mammalian melanoma and mammalian lung carcinoma, comprising administering to said patient, an effective antitumor amount of

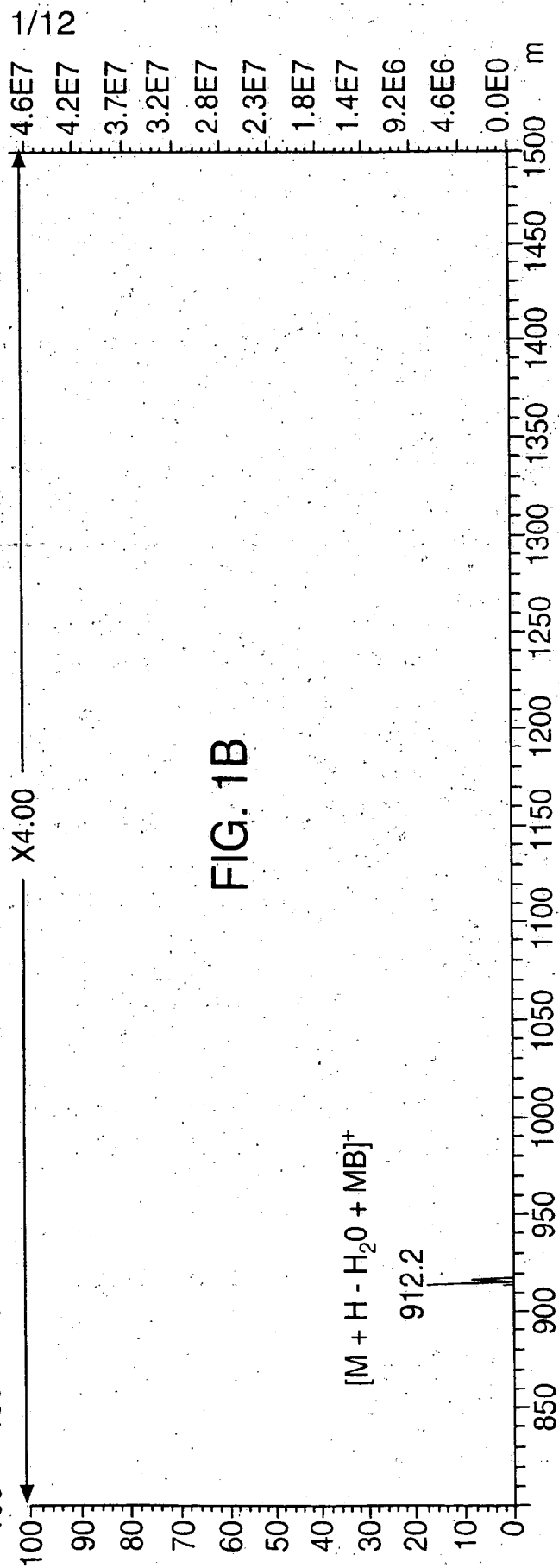
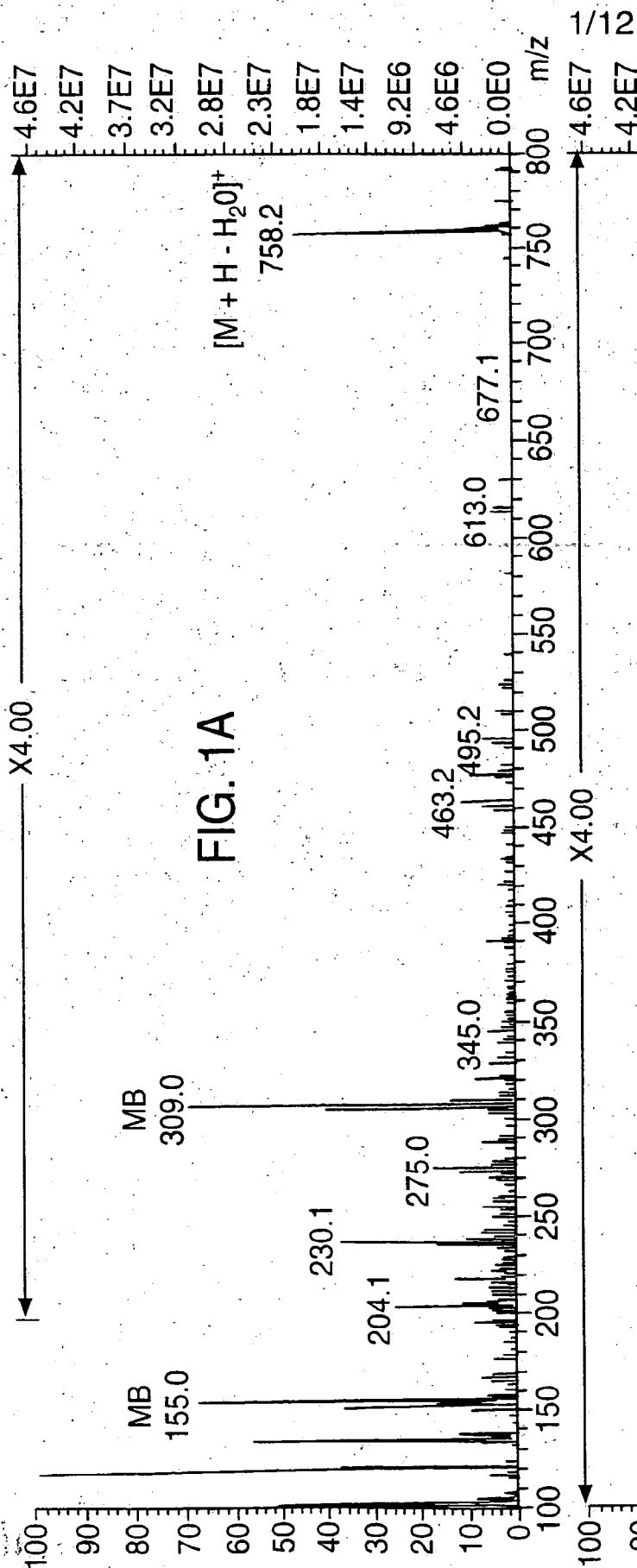
carcinoma, comprising administering to said patient, an effective antitumor amount of the substantially pure compound designated herein as Et 757 and a pharmaceutically acceptable carrier, diluent or excipient.

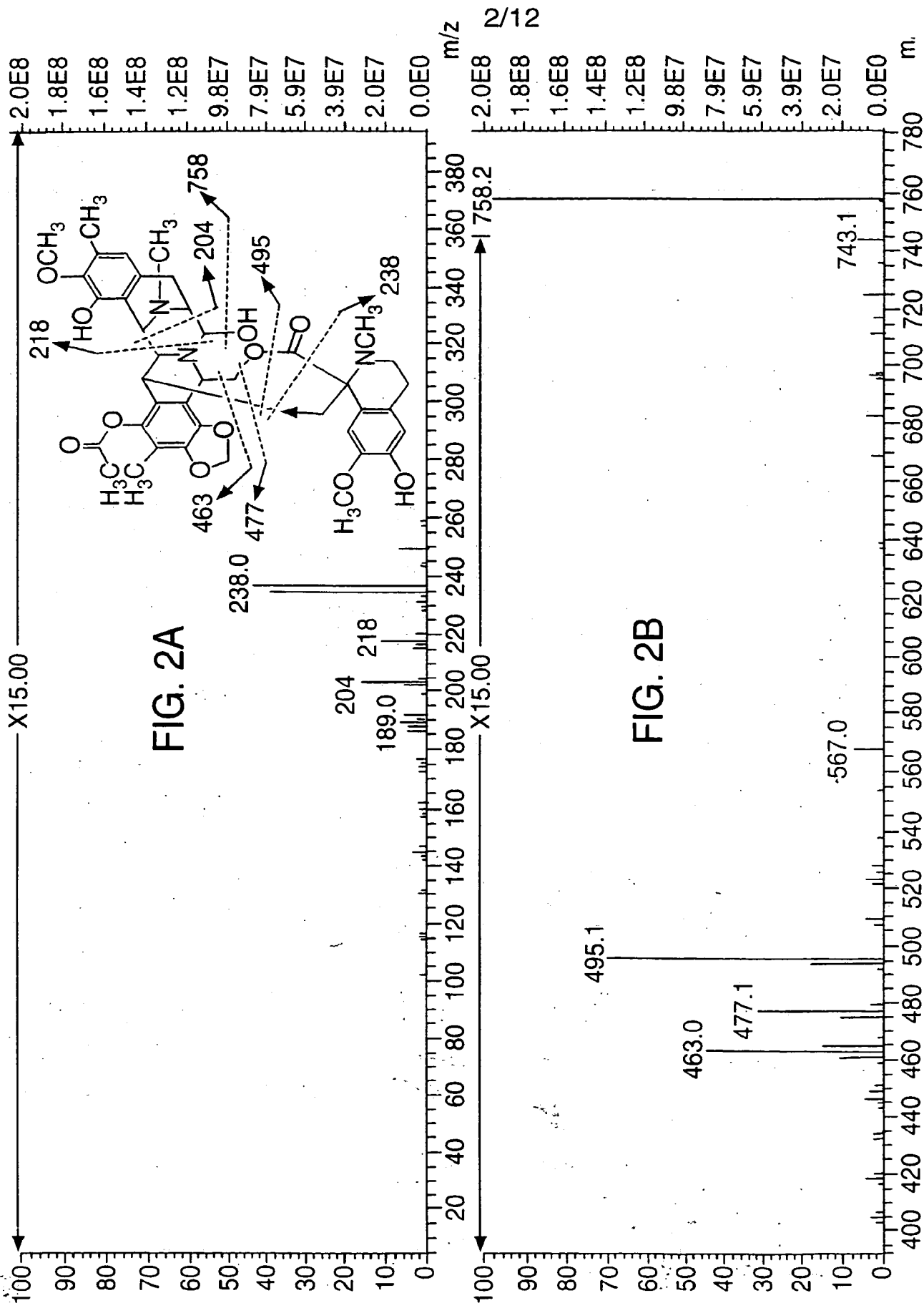
12. A method of treating a patient suffering from a mammalian tumor selected from the group consisting of mammalian leukemia, mammalian melanoma and mammalian lung carcinoma, comprising administering to said patient, an effective antitumor amount of the substantially pure compound designated herein as Boc-Et 729 and a pharmaceutically acceptable carrier, diluent or excipient.

13. A method of treating a patient suffering from a mammalian tumor selected from the group consisting of mammalian leukemia, mammalian melanoma and mammalian lung carcinoma, comprising administering to said patient, an effective antitumor amount of the substantially pure compound designated herein as Iso-Et 743 and a pharmaceutically acceptable carrier, diluent or excipient.

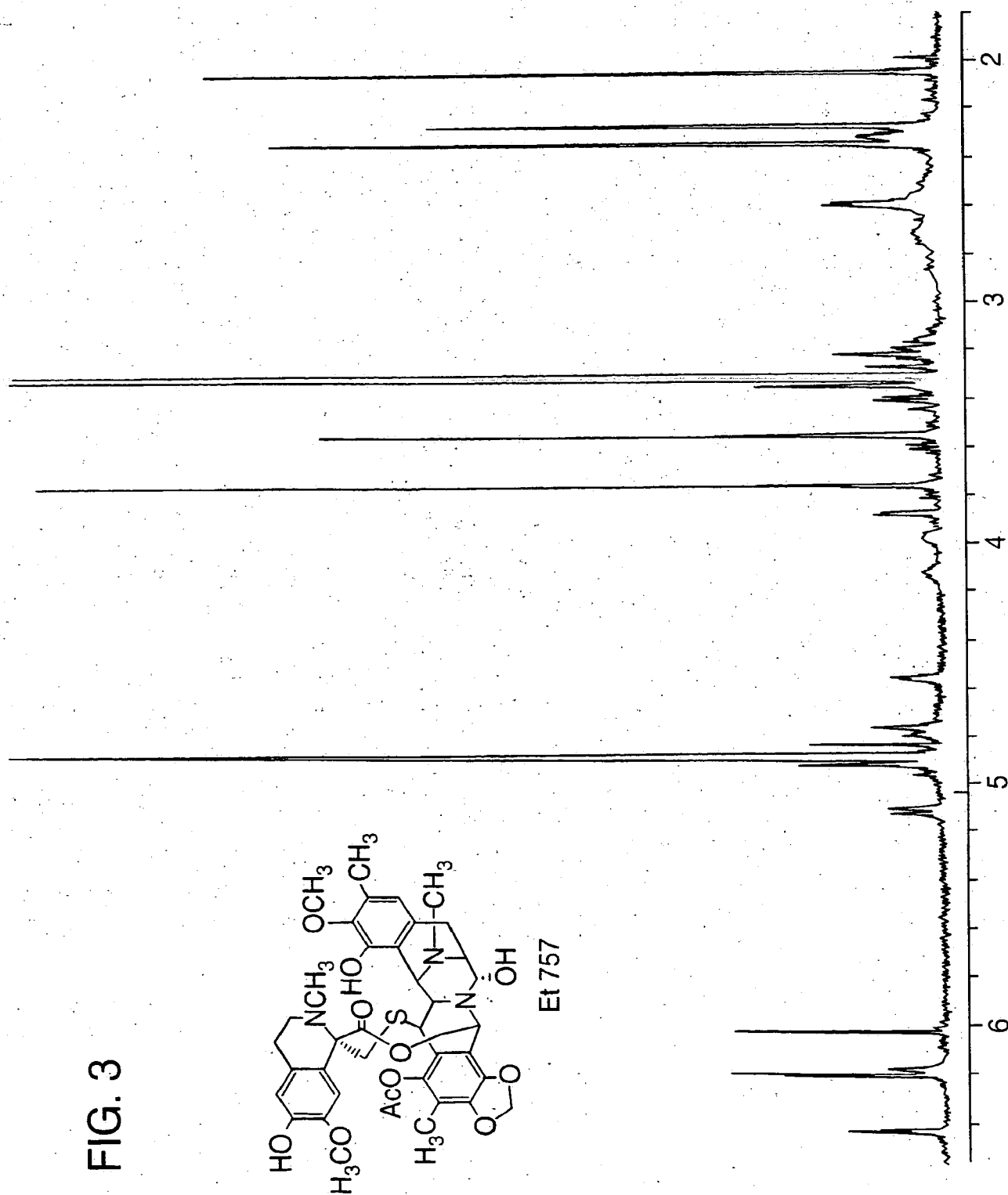
14. A method of treating a patient suffering from a mammalian tumor selected from the group consisting of mammalian leukemia, mammalian melanoma and mammalian lung carcinoma, comprising administering to said patient, an effective antitumor amount of the substantially pure compound designated herein as Et 875 and a pharmaceutically acceptable carrier, diluent or excipient.

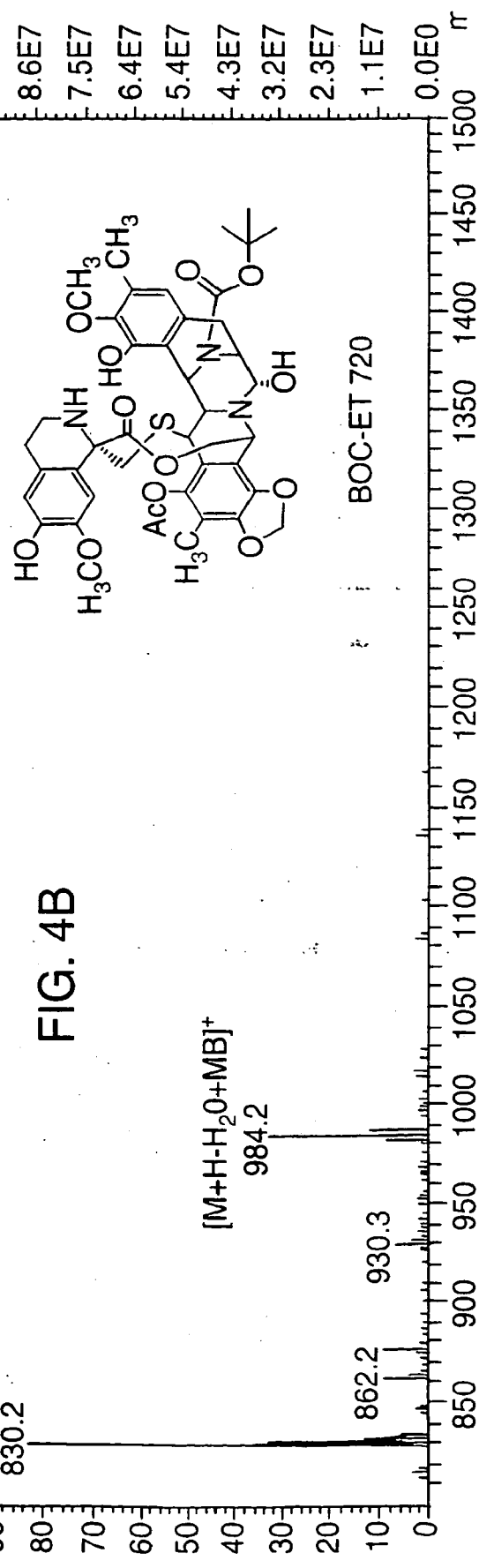
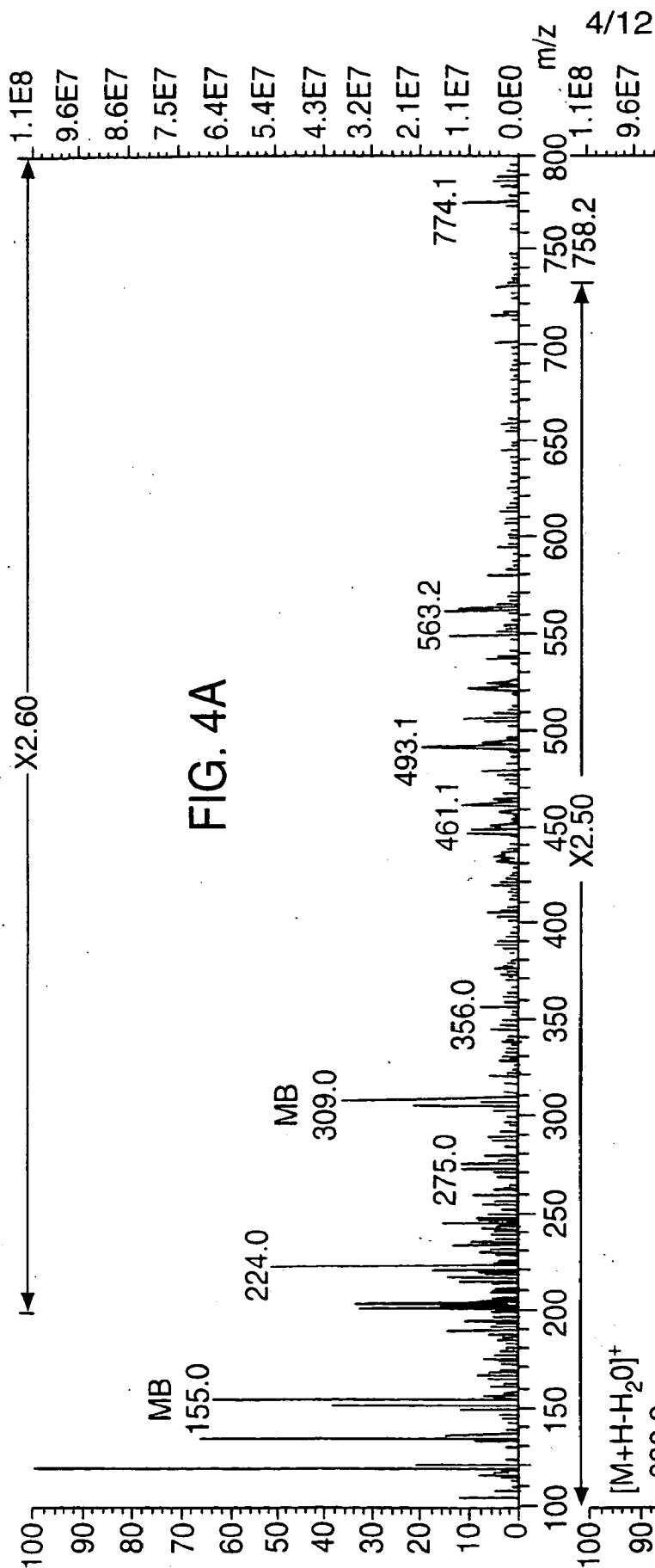
15. A method of treating a patient suffering from a mammalian tumor selected from the group consisting of mammalian leukemia, mammalian melanoma and mammalian lung carcinoma, comprising administering to said patient, an effective antitumor amount of the substantially pure compound designated herein as Et 1560 and a pharmaceutically acceptable carrier, diluent or excipient.

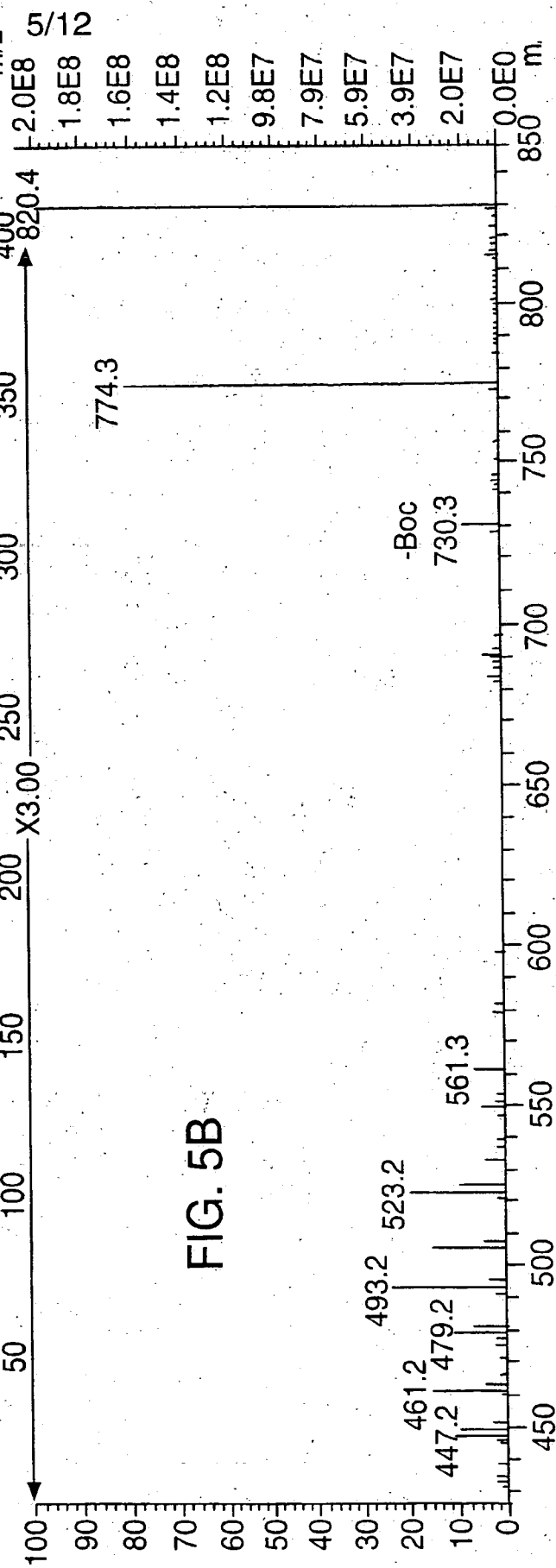
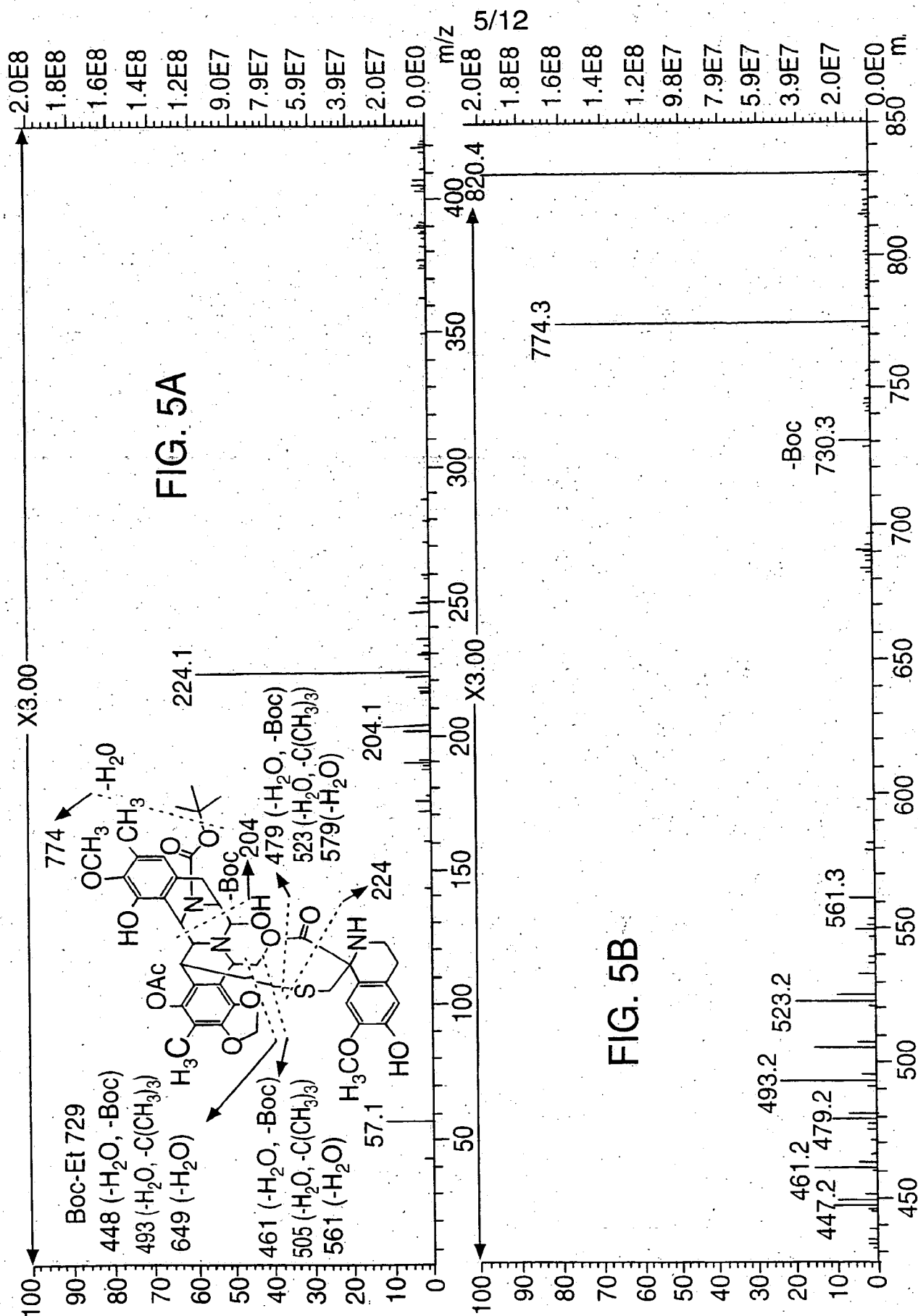




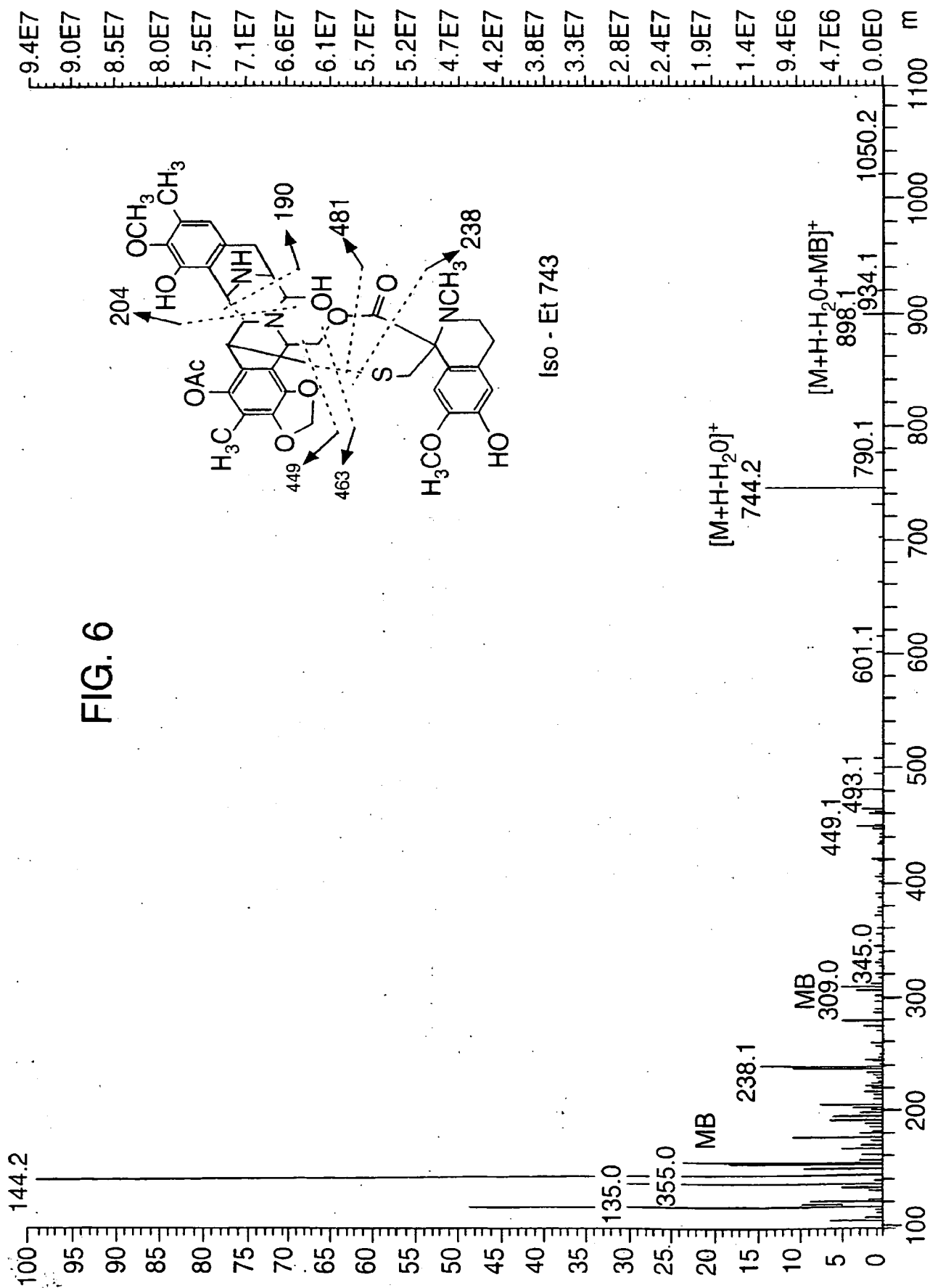
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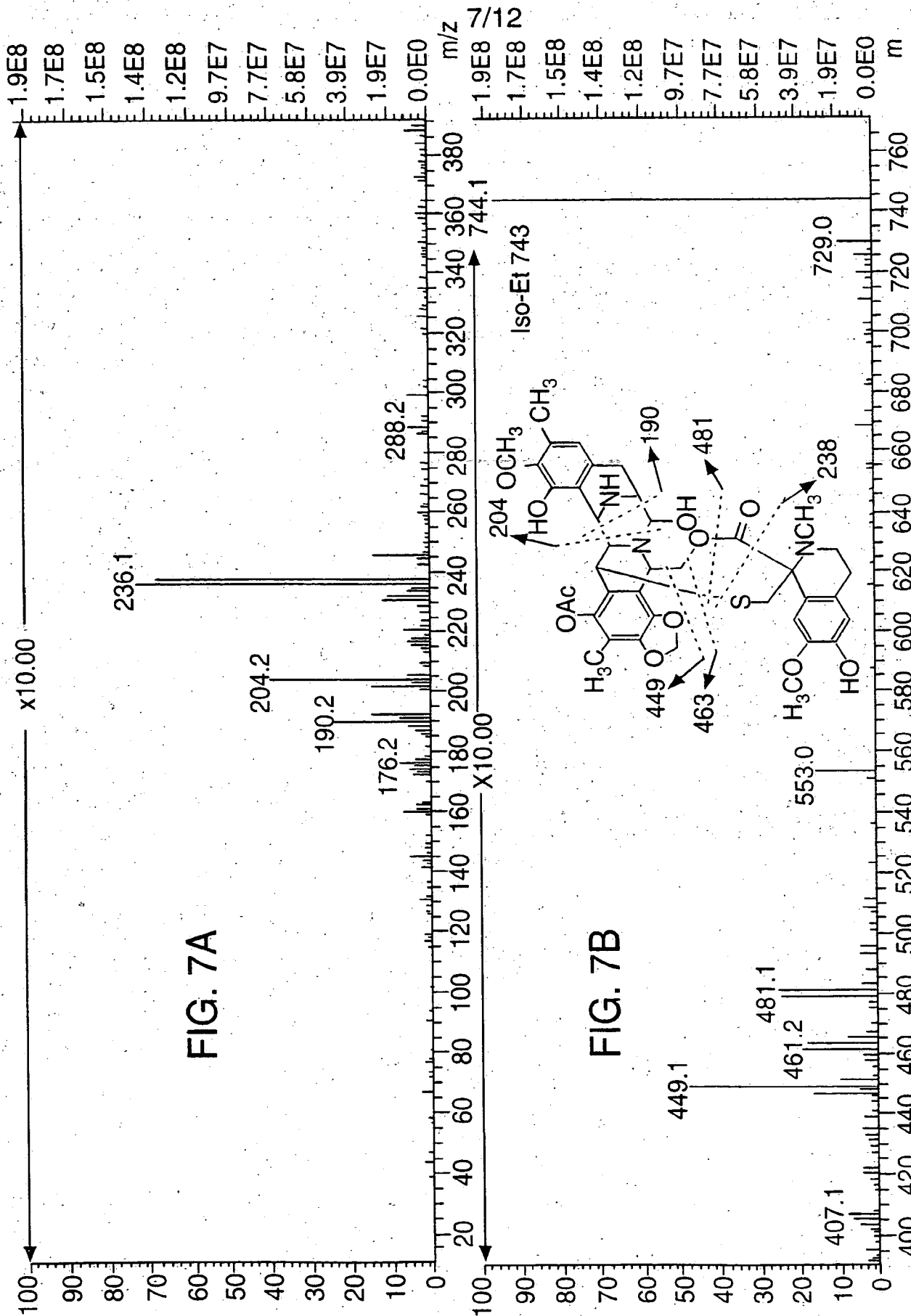






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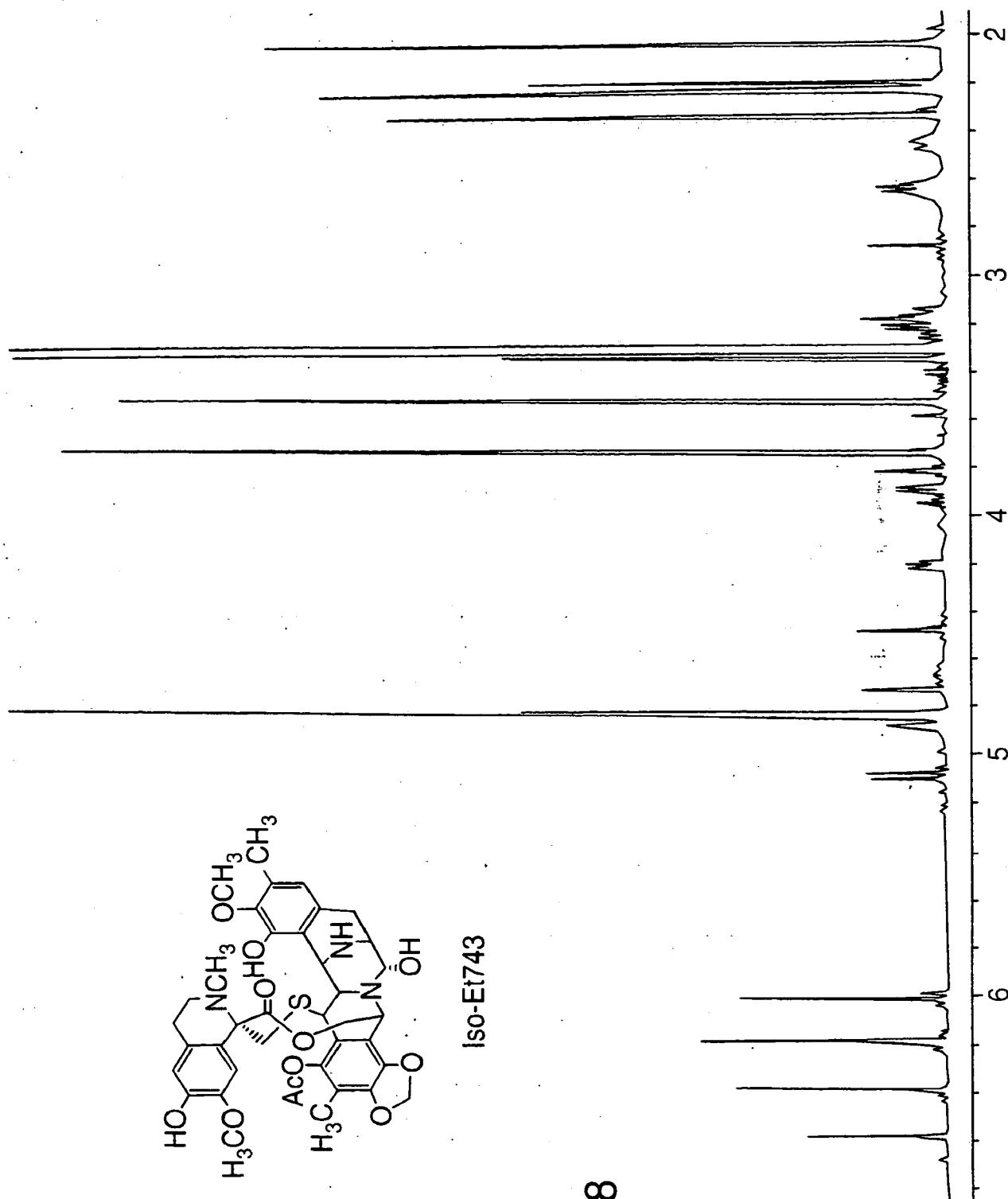


FIG. 8

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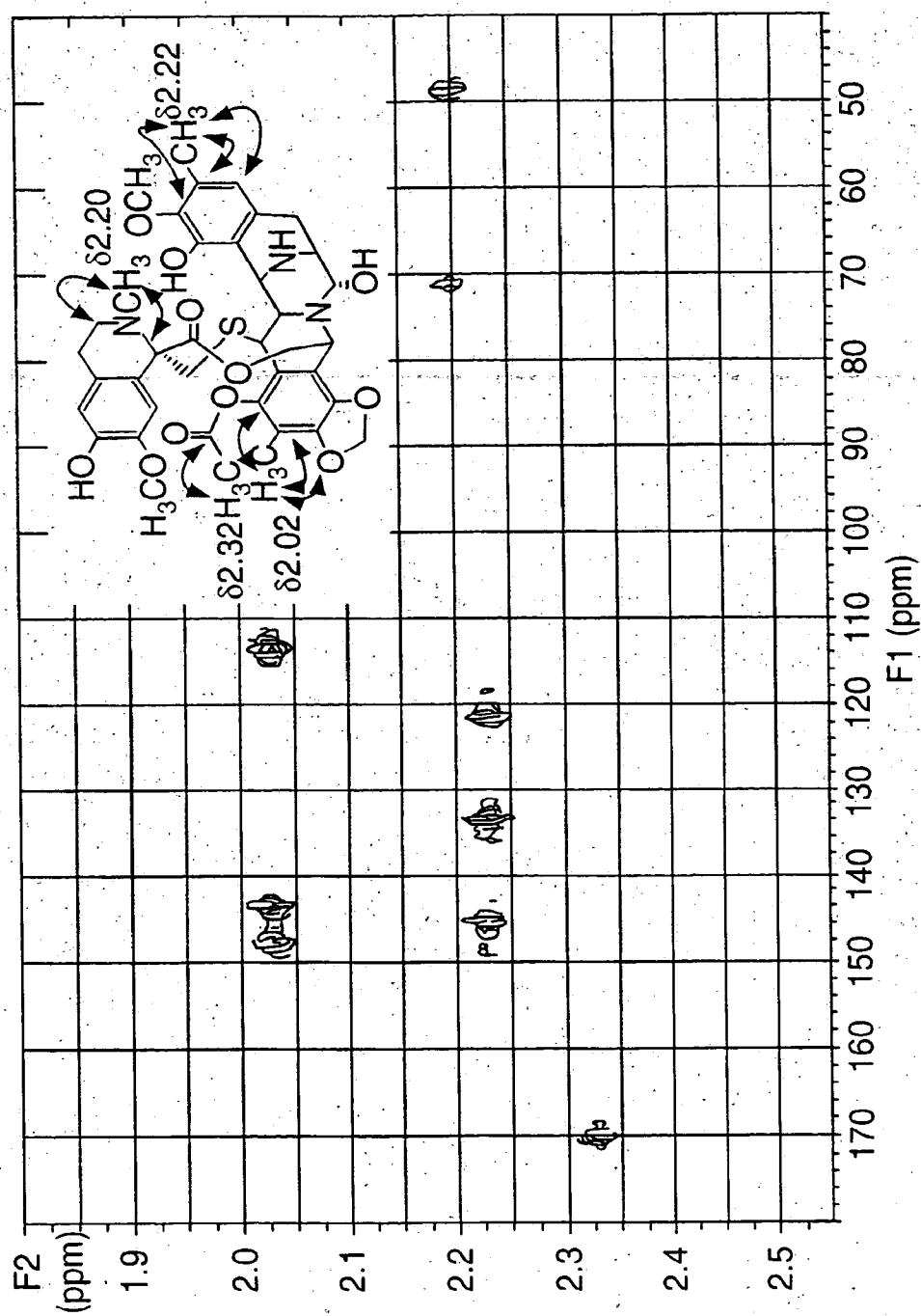
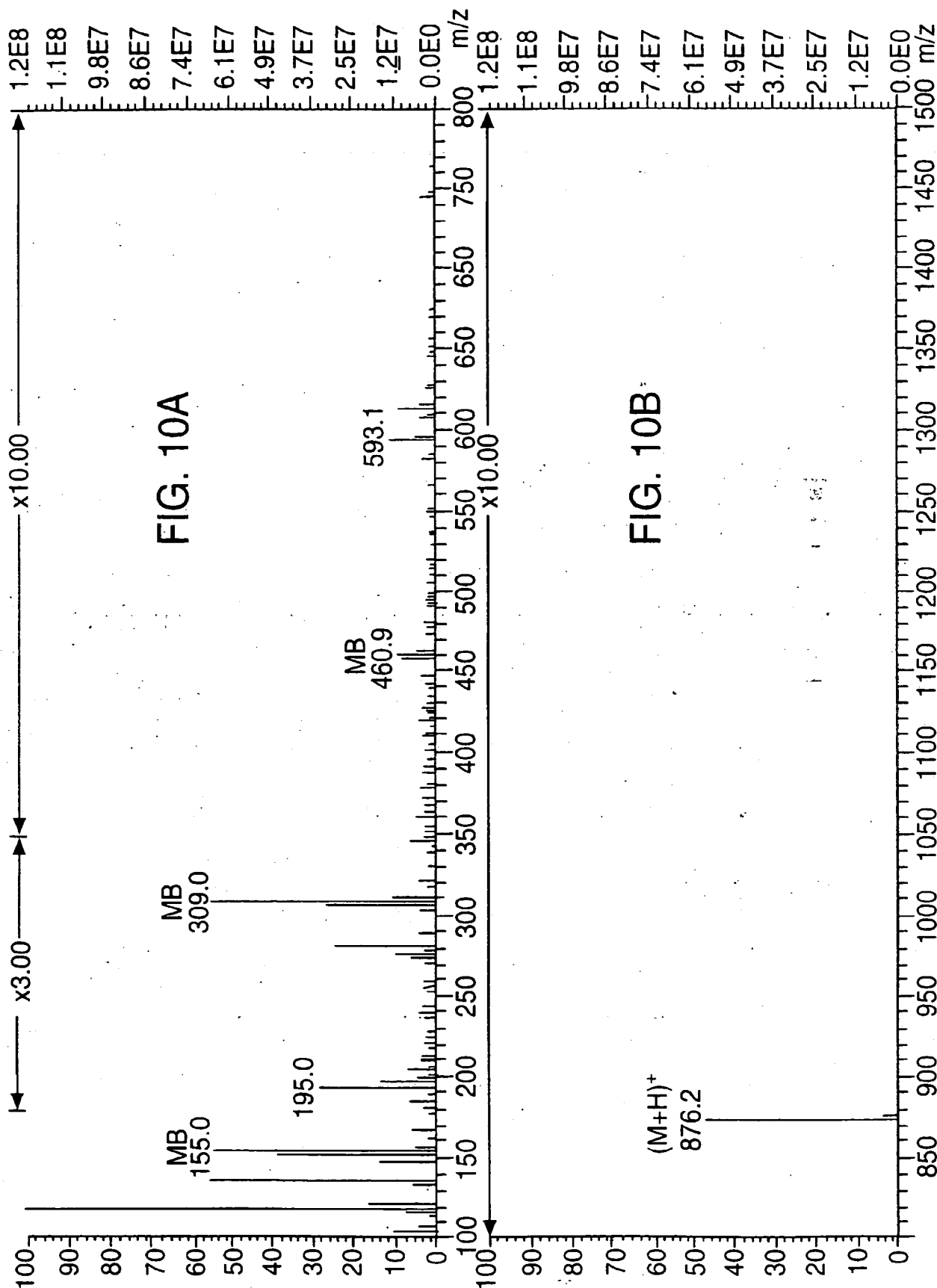


FIG. 9

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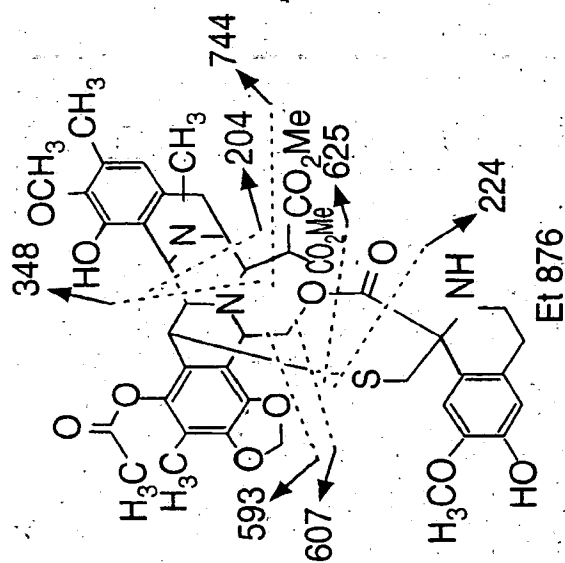
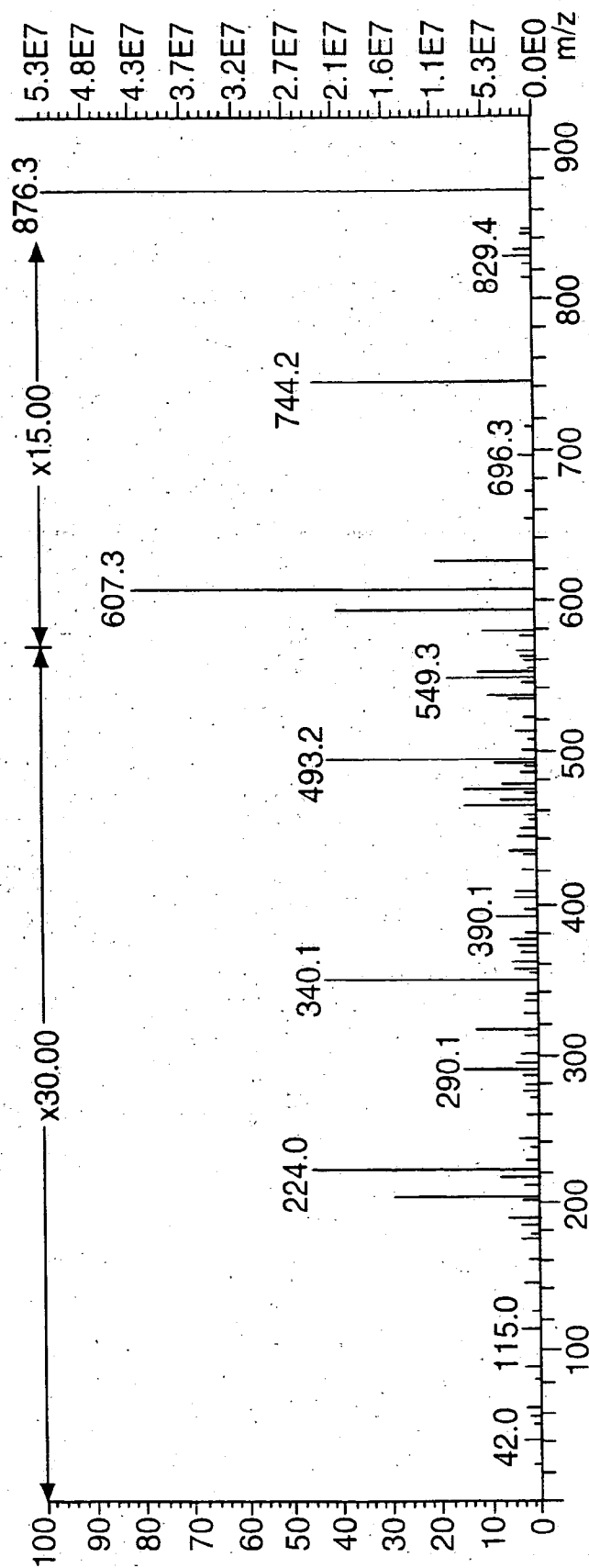


FIG. 11



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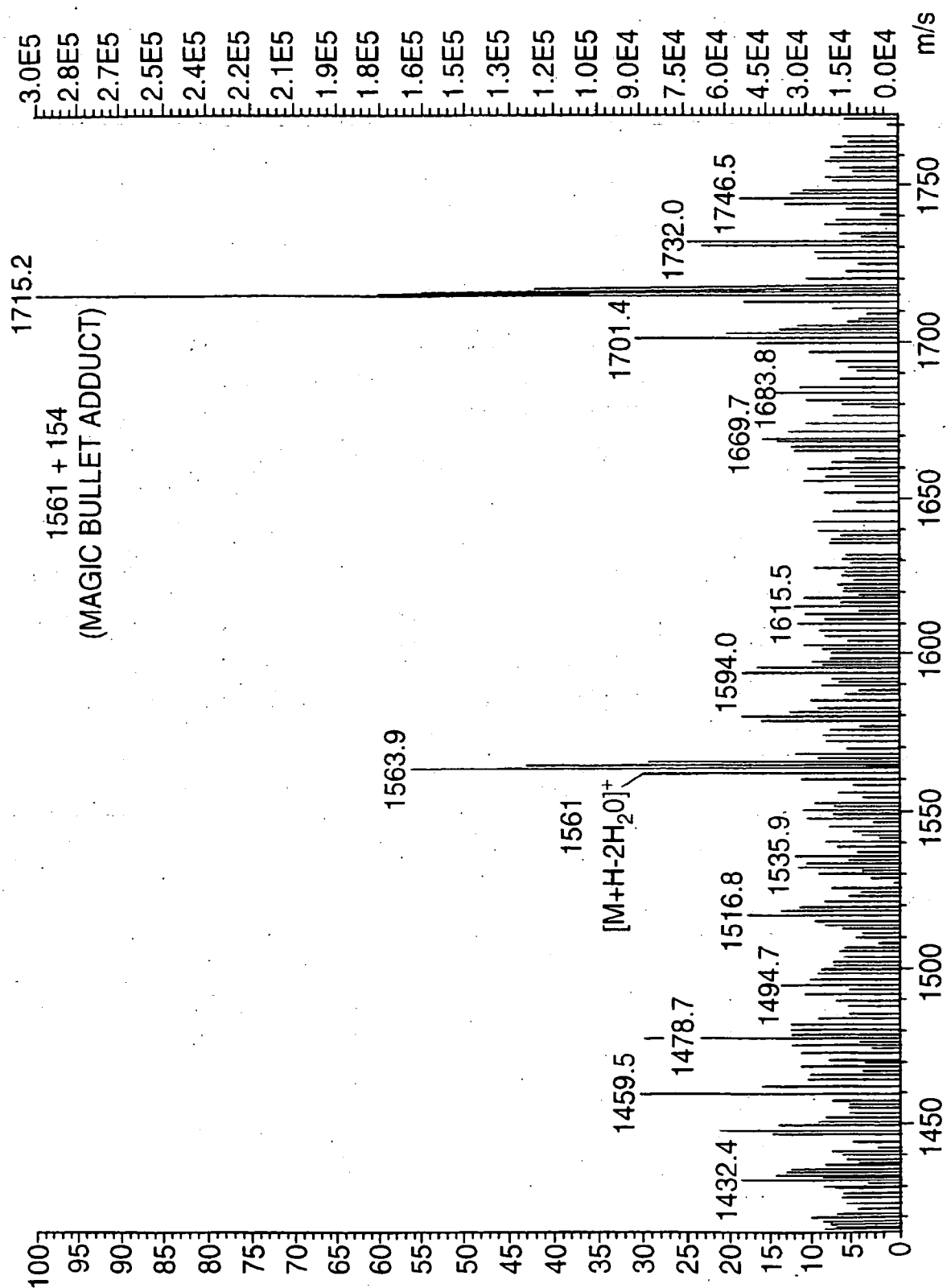


FIG. 12

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/07471**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : A61K 31/495, 31/50; C07D 225/04

US CL : 514/250; 540/466

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/250; 540/466

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|-----------|--|-----------------------|
| A | US 5,721,362 A (COREY et al.) 24 February 1998, see entire document. | 1-15 |
| A | US 5,654,426 A (RINEHART et al.) 05 August 1997, see entire document. | 1-15 |
| A | US 5,478,932 A (RINEHART et al.) 26 December 1995, see entire document. | 1-15 |
| A | US 5,256,663 A (RINEHART et al.) 26 October 1993, see entire document. | 1-15 |
| A | US 5,149,804 A (RINEHART et al.) 22 September 1992, see entire document. | 1-15 |
| A | US 5,089,273 A (RINEHART et al.) 18 February 1992, see entire document. | 1-15 |

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| | |
|---|--|
| * Special categories of cited documents: | * later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
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| *O* document referring to an oral disclosure, use, exhibition or other means | |
| *P* document published prior to the international filing date but later than the priority date claimed | |

Date of the actual completion of the international search

24 JUNE 1999

Date of mailing of the international search report

03 AUG 1999

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